Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
D3-A0206P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/002887	05.03.2004	19.03.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant		
DNAVEC RESEARCH INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☒ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/002887

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/002887

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-5

because:

☒ the said international application, or the said claims Nos. 1-5 relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 1-5 pertain to methods for treatment of the human body by therapy or surgery.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1-5 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/002887

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	6-10	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	6-10	NO
Industrial applicability (IA)	Claims	6-10	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Citations

1. JP 2002-500623 A (The Board of Trustees of the Leland Stanford Junior University), 8 January 2002
2. JP 2000-229883 A (Chemo-Sero Therapeutic Research Institute), 22 August 2000
3. Journal of Immunology, 2002, Vol. 168, No. 1, pages 450-457
4. JP 07-265079 A (Yeda Research and Development Co., Ltd.), 17 October 1995
5. J. Biol. Chem., (2002), Vol. 277, No. 5, pages 3195-3201
6. JP 2003-503313 A (AU, Jessie L.S.), 28 January 2003
7. Nature, (2001), Vol. 412, No. 9, pages 647-651

Explanations

Claims 6-8 and 10

The inventions set forth in claims 6-8 and 10 are not disclosed in any of the documents cited in the international search report and are, therefore, novel. However, these inventions do not involve an inventive step in the light of documents 1-3 cited in the international search report.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Document 1 discloses a gene therapy composition that utilises a vector for expressing sprouty 2 protein and indicates that conditions that block angiogenesis, such as rheumatoid arthritis, are the kind of conditions to which this composition can be usefully applied. Therefore, it would be obvious to a person skilled in the art to essentially apply a vector expressing sprouty 2 protein in the treatment of conditions such as rheumatoid arthritis.

Document 2 discloses a therapeutic agent for the treatment of chronic rheumatoid arthritis having bFGF (FGF2) antagonist as the active ingredient. Moreover, document 3 indicates that in model rats for rheumatoid arthritis, FGF2 promotes neoangiogenesis and neogenesis of osteoclasts, making the symptoms of arthritis deteriorate, and indicates that FGF2 promotes neogenesis of osteoclasts through FGF receptors (1). Furthermore, document 3 suggests that the neutralisation or control of FGF2 is effective in the treatment of rheumatoid arthritis.

Consequently, it would be easy for a person skilled in the art to conceive of selecting a protein or nucleic acid as a substances to block the effects of FGF2, to investigate its therapeutic activity in the treatment of disorders such as rheumatoid arthritis, and to apply it to a method wherein a vector that expresses said protein or nucleic acid is administered.

Claim 9

The invention set forth in claim 9 is not disclosed in any of the documents cited in the international search report and is, therefore, novel. However, the invention

does not involve an inventive step in the light of documents 1-7 cited in the international search report.

Document 1 discloses a gene therapy composition that utilises a vector for expressing sprouty 2 protein and indicates that conditions that block angiogenesis, such as rheumatoid arthritis, are the kind of conditions to which this composition can be usefully applied. Therefore, it would be obvious to a person skilled in the art to essentially apply a vector expressing sprouty 2 protein in the treatment of conditions such as rheumatoid arthritis.

Document 2 discloses a therapeutic agent for the treatment of chronic rheumatoid arthritis having bFGF (FGF2) antagonist as the active ingredient. Moreover, document 3 indicates that in model rats for rheumatoid arthritis, FGF2 promotes neoangiogenesis and neogenesis of osteoclasts, making the symptoms of arthritis deteriorate, and indicates that FGF2 promotes neogenesis of osteoclasts through FGF receptors (1). Furthermore, soluble FGF receptors, sprouty and spred proteins are known as substances that neutralise or control the effects of FGF2, as disclosed in documents 4-7. Therefore, it would be easy for a person skilled in the art to investigate the therapeutic activity of these proteins in the treatment of disorders such as rheumatoid arthritis, and to apply them to a method wherein a vector that expresses these proteins is administered.

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6-8 and 10 pertain to a therapeutic composition for inflammatory diseases associated with bone destruction, such as rheumatoid arthritis having as the active ingredient a vector that codes for a protein or nucleic acid defined by its desired characteristics of "blocking signal transmission through fibroblast growth factor -2 (FGF2)-FGF receptor 1-Ras-Raf-MAP kinase". Of those proteins and nucleic acids having the aforementioned characteristics, only a small proportion are supported by the description in the sense defined in PCT Article 6 and/or can be regarded as having been disclosed in the sense defined in PCT Article 5.

Even taking into consideration the technical knowledge at the time of filing, it is impossible to define the scope of a protein or nucleic acid having such a characteristic as "a protein or nucleic acid for blocking signal transmission through fibroblast growth factor -2 (FGF2)-FGF receptor 1-Ras-Raf-MAP kinase."

Consequently, an opinion has been given concerning the relationship between the blocking of signal transmission (FGF2)-FGF receptor 1-Ras-Raf-MAP kinase and inflammatory diseases associated with bone destruction, and concerning a therapeutic composition for inflammatory diseases associated with bone destruction having as the active ingredient a vector that codes for a protein set forth in claim 9.